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EXAMINER	
LUCAS, J	
ART UNIT	**PAPER NUMBER**
1806	6

DATE MAILED: 10/18/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

Paper No 5

☒ This application has been examined ☒ Responsive to communication filed on 9/4/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-15 are pending in the application.
   Of the above, claims 4 & 9-14 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 6-8 & 15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. Claims 4, and 9-14 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 5.

2. Claims 1-3, 6-8, and 15 will be examined on the merits.

3. The Applicant has claimed no priority under 35 U.S.C. 119 or 120. The priority date of the instant Application is therefore the filing date 12/02/94.

Claim Rejections - 35 USC § 112

4. Claims 1-3, 6-8, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of targeted cell lysis, does not reasonably provide enablement for a method of "inducing an immune response". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. Claims 1-3, and 6-8 are drawn to a method of inducing an immune response in a patient comprising using a bispecific antibody wherein the first binding site recognizes FcγRIII and a second binding site recognizes c-erbB-2. The specification fails to enable one of skill in the art how to induce all of the different forms of immune responses with the bispecific antibody. The specification teaches using the bispecific antibody to induce targeted cytolysis. The specification does not teach all of the responses that could be considered an immune response. Any activity associated with immune function would be considered an

immune response. For example, increased DNA synthesis, secretion of various cytokines or up/downregulation of receptors. This would also include cells of the immune system that do not express FcγRIII or that express FcγRIII but do not lyse cells such as PMNs. A method of inducing an immune response would also comprise vaccinations. The specification does not teach that the bispecific antibodies would be useful as vaccines. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to inducing an immune response with the claimed bispecific antibodies.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

7. Claims 1-3, 6-8, and 15 are rejected under 35 U.S.C. § 103 as being unpatentable over Hsieh-Ma et al. (Cancer Research 1992) or Weiner et al. (Cancer Research 1993) or Ring et al. (Breast Epithelial Antigens 1991) in view of Fanger et al. (Critical Reviews in Immunology 1992).

8. The claims are drawn to a method of inducing an immune response in a patient, comprising a bispecific antibody wherein the first binding site recognizes FcγRIII and a second binding site recognizes the cancer antigen c-erbB-2. The claims are further limited to wherein the bispecific antibody is 2B1 (CRL 10197).

9. Hsieh-Ma et al. teach using 2B1 to induce an immune response in the form of targeted cytolysis. Hsieh-Ma et al. teach that 2B1 could mediate lysis of tumor cells expressing c-erbB-2 in the presence of all blood components found *in vitro* (p.6834 column 2 and 6835 column 1). Hsieh-Ma et al. also teach that 2B1 as an interesting candidate for possible clinical evaluation in patients with c-erbB-2 positive carcinomas (p. 6838). Hsieh-Ma et al. does not teach inducing an immune response in patients with 2B1.

10. Weiner et al. teach using 2B1 to induce an immune response in the form of targeted cytolysis. Weiner et al. teach that 2B1 was effective in inhibiting the growth of human tumor cell line xenografts expressing c-erbB-2 in mice (p.97). Weiner et al. does not teach inducing an immune response in patients with 2B1.

11. Ring et al. (Breast Epithelial Antigens 1991) teach using 2B1 to induce an immune response in the form of promoting the lysis of tumor cells expressing c-erbB-2 by human large granular lymphocytes and macrophages *in vitro* (p.91). Ring et al. state: "we look forward to future evaluation of 2B1...in animal models and human clinical trials. Ring et al. does not teach using 2B1 to induce an immune response in patients.

12. Fanger et al. teach a review of using bispecific antibodies to induce an immune response in the form of targeted cytolysis in human patients. Fanger et al. teach using bispecific antibodies in targeted cytolysis wherein one the binding sites binds FcγRIII. The references cited within Fanger et al. teach the methods of administrating bispecific antibodies as well as, doses, duration of treatment, etc.

13. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the bispecific antibody 2B1 as taught by Hsieh-Ma et al., Weiner et al. and Ring et al. to induce an immune response in patients in the form of target cytolysis as taught by Fanger et al. One of ordinary skill in the art at the time the invention was made would have been motivated to use 2B1 in patients because Hsieh-Ma et al., Weiner et al. and Ring et al. teach that 2B1 is effective in the targeted cytolysis of tumor cells, and Fanger et al. teach bispecific antibody mediated targeted cytolysis is a promising form of cancer treatment.

No Claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Lucas whose telephone number is (703) 305-6838. The examiner can normally be reached on M-T from 8:00am to 6:00pm EST.

15. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-7362 or 305-7939.

16. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John Lucas, PhD

11 October 1996

LILA FEISEE
PRIMARY EXAMINER
GR 1800